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ORIGINAL ARTICLE

Differential presentation of hypersensitivity reactions to carboplatin and oxaliplatin: Phenotypes, endotypes, and management with desensitization

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Abstract

Background: Drug hypersensitivity reactions (DHRs) to platinum-based drugs are heterogenous and restrict their access, and drug desensitization (DD) has provided a ground-breaking procedure for their re-introduction, although the response is heterogeneous. We aimed to identify the phenotypes, endotypes, and biomarkers of reactions to carboplatin and oxaliplatin and their response to DD.

Methods: Seventy-nine patients presenting with DHRs to oxaliplatin ($N = 46$) and carboplatin ($N = 33$) were evaluated at the Allergy Departments of two tertiary care hospitals in Spain. Patient symptoms, skin testing, biomarkers, and outcomes of 267 DDs were retrospectively analyzed.

Results: Oxaliplatin-reactive patients presented with type I (74%), cytokine release reaction (CRR) (11%), and mixed (Mx) (15%) phenotypes. In contrast, carboplatin

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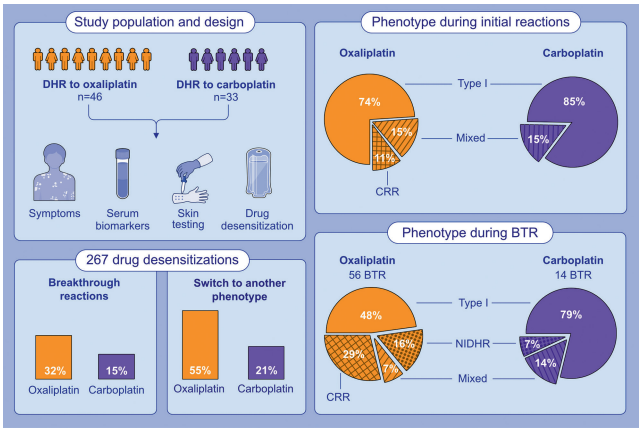
reactive patients presented with predominantly type I (85%) and Mx (15%) but no CRRs. Out of 267 DDs, breakthrough reactions (BTRs) to oxaliplatin occurred twice as frequently as carboplatin (32% vs. 15%; $p < .05$). Phenotype switching from type I to another phenotype was observed in 46% of oxaliplatin DDs compared to 21% of carboplatin DDs. Tryptase was elevated in type I and Mx reactions, and IL-6 in CRR and Mx, indicating different mechanisms and endotypes.

Conclusion: Carboplatin and oxaliplatin induced three different types of reactions with defined phenotypes and endotypes amendable to DD. Although most of the initial reactions for both were type I, oxaliplatin presented with unique CRR reactions. During DD, carboplatin reactive patients presented mostly type I BTR, while oxaliplatin-reactive patients frequently switched from type I to CRR, providing a critical difference and the need for personalized DD protocols.

KEYWORDS
carboplatin, desensitization, endophenotype, hypersensitivity, oxaliplatin



GRAPHICAL ABSTRACT

Carboplatin reactions are type I IgE-mediated with few mixed phenotype, while oxaliplatin reactions are type I IgE-mediated, CRR and mixed phenotypes. Desensitization is safe and effective for both platins regardless of phenotypes. Breakthrough reactions during desensitization are type I for carboplatin with tryptase elevations. Oxaliplatin reaction can undergo phenotype switching from type I to CRR and mixed with IL-6 elevations. Abbreviations: BTR, breakthrough reaction; CRR, cytokine release reaction phenotype; IL-6, interleukin 6; NIDHR, non-immediate drug hypersensitivity reaction.

1 | INTRODUCTION

Platinum-based drugs such as carboplatin, cisplatin, and oxaliplatin are first-line chemotherapeutic agents used to treat ovarian, breast, prostate, colon, and lung cancers, and their use is limited by DHRs. While re-exposure to the inciting drug after DHR is not recommended due to the potential increase in the severity of subsequent reactions, DD has emerged as a powerful treatment modality permitting safe re-exposure. The phenotypes of DHRs amenable to desensitization include type 1 IgE, non-IgE-mediated reactions including anaphylaxis, non-severe delayed type IV T cell-mediated reactions, and more recently cytokine release reactions and mixed reactions (Mx) have been shown to be prevented by DD.[1–4]

For carboplatin, the risk of DHRs is 27% after 6 exposures and BRCA (BReast CAncer gene) carriers may have earlier sensitization.[5,6] For oxaliplatin, the risk of DHRs is 41% after 8 or more exposures.[6] The use of premedications such as antihistamines and steroids has not provided protection against anaphylaxis when re-introducing the offending medications in sensitized patients.[7]

DD is an immunotherapy procedure which takes advantage of inhibitory mast cells mechanisms allowing patients to remain on first-line therapy and increasing their quality of life and life expectancy.[8–11] Accurate phenotyping, endotyping, and assessment of biomarkers have permitted risk stratification in reactive patients and the development of personalized DD protocols.[12–14]

Carboplatin and oxaliplatin contain central platinum atom cores (Figure S1); in addition, carboplatin has two primary ammonia groups

that are not present in oxaliplatin. These molecular differences may influence immune sensitization and IgE cross-reactivity.[4,15] Based on a study of serum specific IgE in carboplatin and oxaliplatin-reactive patients, those with oxaliplatin reactions demonstrated polyclonal IgEs cross-reactive with carboplatin and cisplatin while carboplatin-allergic patients had little cisplatin and oxaliplatin cross-reactive IgEs.[15]

Reactions to carboplatin are typically type I, and recent description of reactions to oxaliplatin indicates that in addition to type 1, CRR, and Mx reactions are also frequent.[4,16] Oxaliplatin-reactive patients presenting with initial type I phenotype can switch during BTR to Mx and CRR reactions, a novel finding which has not been confirmed in large studies and for which there is little mechanistic understanding.[4]

The purpose of this study was to identify phenotypes, endotypes, and biomarkers of carboplatin and oxaliplatin of initial reactions and BTRs during DD in a cohort of patients treated in two large referral centers to further understand differences and personalized approach to DD.

2 | MATERIALS AND METHODS

The collaboration between Dr. Balmis General University Hospital, Alicante-Spain and Marqués de Valdecilla University Hospital, Santander-Spain was approved by each institutes Ethics Committee. Between January 2018 and June 2020, 79 patients were retrospectively identified for DHRs to carboplatin and oxaliplatin and were desensitized. All patients signed the informed consent before each procedure, which contemplated the use of data for scientific purposes. Exclusion criteria included non-immediate severe cutaneous adverse reactions with systemic symptoms (SCARS).

2.1 | Classification of reactions

Patients were phenotyped based on skin testing, biomarkers, and symptoms and classified into four different groups: type I, CRR, Mx, and non-immediate drug hypersensitivity reactions (NIDHRs). Type I phenotype symptoms included pruritus, urticaria, angioedema, nasal congestion, sneezing, wheezing, cough, throat tightness, tongue swelling, hypotension, seizures, and syncope; positive skin tests and/or significant increase in tryptase levels. CRR symptoms included chest pain, back pain, abdominal pain, headache, rigors, chills, numbness/weakness, hypertension, hypotension, fever, and/or increased IL-6 levels. Mx reactions involved a combination of type I and CRR symptoms and biomarkers. NIDHRs presented as delayed symptoms occurring more than 6 h after treatment.[17,18] The severity of the reactions was classified according to Brown's grading system of 1 through 3 with grade 1 (G1) involving one organ system, grade 2 (G2) involving 2 or more organ systems and grade 3 (G3) involving one or more organ systems and changes in vital signs.[19]

2.2 | Skin testing

Skin testing (ST) was performed at least 2 weeks after the initial DHR to avoid false negatives. Oxaliplatin 5 mg/mL and carboplatin 10 mg/mL were used for prick testing and 1:100, 1:10 and 1:1 dilutions for intradermal testing. A positive test was defined by a wheal of 3 mm or greater than the negative control (normal saline). Histamine (10 mg/mL) was used as a positive control.

2.3 | Desensitization protocols

The desensitization protocols were adopted from the Brigham and Women's Hospital Drug Hypersensitivity and Desensitization Center and included 4 bags/16 steps, 3 bags/12 steps, and 2 bags/8 steps.[1] There were different dilutions in each bag, starting at 1/1000 in the 4 bags protocol, 1/100 in the 3 bags protocol, and 1/10 in the 2 bags protocol. Each step consisted of escalating doses 2 to 2.5 times every 15 min, until reaching the target dose at the end of the procedure, administered in the regular concentration.

2.4 | Premedications

Thirty minutes prior to DD, all patients received cetirizine 10 mg orally (PO) and ranitidine 50 mg intravenously (IV). In addition, symptom-specific medications were administered: Aspirin (ASA) 300 mg PO for flushing; montelukast 10 mg PO for bronchospasm/chest tightness; COX-1 inhibitors (ibuprofen 600 mg PO), paracetamol (1000 mg IV), intravenous fluids, and opioids (tramadol 100 mg IV) for chills, rigors, fever, and pain; and alprazolam 0.5 mg PO for anxiety. β-adrenergic blocking medications were held for 24 h prior to DD.[20]

2.5 | Treatment of breakthrough reactions during desensitization

Treatment of BTRs during DDs included stopping the infusion and using symptom-specific medications. Upon symptom resolution, the infusion was resumed, unless the patient preferred to discontinue. Shared decision-making was done between the attending allergist and the patient.

2.6 | Biomarkers

Tryptase and IL-6 levels were drawn 30 to 120 min post reaction (Tryptase fluoroimmunoassay, Thermo Fisher Scientific, Uppsala, Sweden; and Elecsys IL-6 Immunoassay; Roche Diagnostics). Tryptase levels greater than 11.4 μg/L and values equal to or greater than *baseline X 1.2 + 2* were considered significant elevations.[21,22] IL-6 values greater than 10 pg/mL were considered elevated.

To determine statistical differences between the two groups, a two-sided Welch *t* test with a 95% CI was used for the continuous variables and a chi-square test was used for the categorical variables. The mean and SD for each variable, as well as the number and the percent for each categorical variable, were calculated and reported. To compare the means of the baseline biomarkers and the means during BTRs, the Student's *t* test was used for related samples. An ANOVA test was used for the analysis of the means of the biomarkers according to the phenotypes. All statistical analyses were performed using the IBM SPSS Statistics for Windows, version 27 (IBM Corp.).

3 | RESULTS

3.1 | Patient demographics, initial reaction phenotypes, severity, and skin testing

The majority of 79 patients were female, 32 over 33 (97%) with DHRs to carboplatin and 22 over 46 (48%) with DHRs to oxaliplatin. The mean age was 55 years for carboplatin and 62 years for oxaliplatin ($p = .005$). Patients in the oxaliplatin group had more advanced cancer stages ($p = .005$). Atopy was observed in 13/33 (39%) patients with DHRs to carboplatin and in 8/46 (17%) with DHRs to oxaliplatin ($p = .04$) (Table 1).

Initial type I reactions were most frequent in both groups. Oxaliplatin-reactive patients presented three different phenotypes: type I 34 (74%) patients, CRR 5 (11%) patients, and Mx 7 (15%) patients. Carboplatin initial DHRs were type I 28 (85%) and Mx 5 (15%) reactions, which is increased from other studies.[8] NIDHR was not observed during initial reactions for either drug (Figure 1). The average lifetime exposure before the initial DHR was 7 for carboplatin and 9 for oxaliplatin.

The severity of reactions in type 1 initial DHR for 28 carboplatin patients was 7 (25%) G1, 13 (46%) G2, and 8 (29%) G3. Patients with G3 reactions were more observed in carboplatin Mx phenotype (4 patients, 80%). The severity of reactions for 34 oxaliplatin patients with initial type I DHR was 5 (15%) G1, 18 (53%) G2, and 11 (32%) G3. Five oxaliplatin patients with initial phenotype CRR had severe reactions (40% G2 and 60% G3), and all Mx phenotype reactive patients had G3 reactions (7, 100%) (Figure 1).

We performed skin tests on 76 patients (96%), of which 24/32 (75%) were positive for carboplatin and 40/44 (91%) for oxaliplatin. (Table 1). Of the 32 patients who underwent carboplatin intradermal ST, 10 (31%) patients developed a skin induration at the injection site 24–48 h after testing. This was also observed in 8/44 (18%) patients who underwent oxaliplatin ST. Additionally, seven carboplatin patients and three oxaliplatin patients developed a superficial ulcer at the injection site 5–8 days post ST. These patients were treated with topical corticosteroids (mometasone furoate) twice a day for 7 days with complete resolution of symptoms.

TABLE 1 Demographics and patient characteristics.

	Carboplatin ($n = 33$)	Oxaliplatin ($n = 46$)
Sex; *n* (%)		
Female	32 (97)	22 (48)*
Male	1 (3)	24 (52)
Age (years); mean + SD	54.7 + 10.9	62 + 11.2*
Race/ethnicity; *n* (%)		
Caucasians	30 (91)	46 (100)*
Hispanic	3 (9)	0
Cancer type, *n* (%)		
Gyn cancer	31 (94)	2 (4)*
Lung	1 (3)	
Rectal	1 (3)	8 (17)*
Colon	0	28 (61)*
Gastric	0	4 (9)*
Esophageal	0	2 (4)*
Gallbladder	0	1 (2)*
Pancreas	0	1 (2)*
Cancer stage; *n* (%)		
I–III	18 (54)	10 (22)*
IV	14 (42)	34 (74)*
NR	1 (3)	2 (4)
Recurrent cancer; *n* (%)		
Yes	26 (79)	35 (76)
Metastatic cancer; *n* (%)		
Yes	20 (61)	44 (96)*
Atopy; *n* (%)	13 (39)	8 (17)*
Allergic rhinitis/asthma	13 (100)[a]	1 (12)*,[b]
Food allergies	2 (15)[b]	3 (37)
Metal contact dermatitis	0	2 (25)
Acute urticaria	2 (15)[c]	3 (37)
History of drug adverse reactions; *n* (%)	4 (12)	6 (13)
Genes BRCA done, *n* (%)	17 (51)	
Positive BRCA 1	5 (29)	
Positive BRCA 1&2	1 (6)	
Negative	11 (65)	
Previous exposures; median (range)	7.3 (1–15)	8.5 (1–22)
Severity of the initial reaction; *n* (%)		
G1	7 (21)	5 (11)
G2	14 (42)	20 (43)
G3	12 (36)	21 (46)
Skin test done; *n* (%)	32 (97)	44 (96)
Positive	24 (75)	40 (91)
Baseline tryptase level (μg/mL); (# of tests done) mean + SD	(36) 4.9 ± 3.1	(34) 4.4 ± 1.5

TABLE 1 (Continued)

	Carboplatin ($n=33$)	Oxaliplatin ($n=46$)
Tryptase level during initial reaction (μg/mL); (# of tests done) mean + SD	(12) 11.2 ± 7.6[d]	(21) 7.8 ± 2.9[d]
Baseline IL-6 level (pg/mL); (# of tests done) mean + SD	(13) 6.6 ± 4.6	(7) 4.6 ± 2.4
IL-6 level during BTR (pg/mL); (# of tests done) mean + SD	(2) 35.6 ± 47.8[d]	(10) 1225.8 ± 3919.9[d]
Desensitizations	90	177
Completed without reactions (%)	76 (84)	121 (68)
Reacted during the treatment (%)	14 (15)	56 (32)*

[a]Two patients had concomitantly allergic rhinitis and asthma.

[b]Had concomitantly food allergies and allergic rhinitis.

[c]Both patients had concomitantly urticaria and allergic rhinitis.

[d]Significant elevation. Tryptase normal value <11.4 μg/L and IL-6 normal value <10 pg/mL.

*$p \leq .05$.

3.2 | Premedication

Based on the symptoms during the initial reaction, all protocols in carboplatin-allergic patients (90 protocols in 33 patients) were premedicated with cetirizine and ranitidine; in addition, ASA was administered in 68 (76%) protocols, montelukast in 53 (59%), alprazolam in 47 (52%), ibuprofen in 1 (3%), and prednisone in 1 (3%). Additional premedication was added between steps due to reactions during DD in 10 (11%) protocols (H1 blockers in 70%, montelukast in 40%, and H2 blockers in 20%), and it was necessary to adjust the premedication in 3 (3%) protocols (adding β2 agonists in 33%, ASA in 33%, and alprazolam in 33%).

Regarding oxaliplatin-reactive patients, all protocols (177 protocols in 46 patients) were premedicated with cetirizine and ranitidine; in addition, montelukast was administered in 145 (82%) protocols, ASA in 104 (59%), IV fluids in 17 (10%), alprazolam in 13 (7%), ibuprofen in 6 (3%), and prednisone in 2 (1%). It was necessary to add premedication between steps in 70 (39%) protocols (H1 blockers in 57%; paracetamol in 33%, IV fluids in 26%, montelukast in 17%, H2 blockers in 16%, ibuprofen in 14%; ASA in 9%, prednisone in 6% and alprazolam in 1%); it was also necessary to adjust premedication in 12 (7%) protocols (premedication was added to 9: ASA in 56%, IV fluids in 22%, montelukast 11% and alprazolam in 11%, premedication was reduced in 3 protocols in which alprazolam was suspended).

3.3 | Desensitization outcomes

A total of 267 protocols were reviewed and 263 DD were completed (98%), while 4 protocols were not completed in three patients. One carboplatin-allergic patient had BTR with mild symptoms (G1) and decided not to continue with DD. Two patients developed G3 BTRs with elevated tryptases and required epinephrine, 1 patient with elevated total IgE 5810 IU/mL had 2 separate anaphylactic reactions during 2 DD protocols. This patient continued with 4 subsequent DD without BTRs after omalizumab 600 mg was administered 2 weeks before DD and 300 mg 24 h before each DD. The other patient decided not to continue with DD (Table S1).

BTRs during DD were twice as frequent with oxaliplatin compared to carboplatin (32% vs 15%; $p = .01$) (Figures 2 and 3). Seventy four percent of the patients who experienced BTRs had positive ST. NIDHRs were reported after 10 DDs, 1 to carboplatin and 9 to oxaliplatin (Figures 2 and 3; Figure S2 and Table S2).

3.4 | Phenotype switching and delayed reactions

Phenotype switching occurred in 3 carboplatin patients and 16 oxaliplatin patients ($p = .01$). Many patients who changed phenotype initially presented with a type I (Figures 2 and 3).

Of 28 carboplatin-allergic patients with initial type I phenotype, who had 78 DDs, BTRs occurred in 14 patients, 79% remained the same initial phenotype, phenotype conversion rate was observed in 21%, with 14% of patients switching to a Mx and 7% to NIDHR (Figure 2 and Figure S2).

Thirty-four type 1 oxaliplatin patients had 139 DDs, 43 BTRs occurred with 54% type 1 phenotype and phenotype switching in 46% with 19% to a CRR phenotype, 9% to Mx, and 18% to NIDHR (Figure 3 and Figure S2). Seven patients with initial Mx had 24 DD, 10 BTRs occurred with a phenotype conversion rate of 100%: 40% switched to type I and 60% switched to CRR (Figure 3 and Figure S2). Five patients with initial CRR had 14 DD and 3 BTRs occurred, 67% continued with the initial phenotype, and a phenotype conversion rate of 33% to a NIDHR phenotype (Figure 3 and Figure S2).

Non-immediate BTRs were observed in six patients after completing 10 DDs. One patient with an initial type I reaction developed urticaria 12 h post carboplatin DD which resolved with cetirizine 10 mg PO for 3 days. This was also observed in one patient with an initial type I reaction to oxaliplatin who developed urticaria 24 h post infusion on four separate occurrences, which resolved with cetirizine 10 mg PO for 3 days. Another oxaliplatin-reactive patient exhibited pruritus and angioedema 6 h post infusion, which resolved with cetirizine 10 mg PO for 3 days. Facial flushing developed 12 h post oxaliplatin DD was observed in one patient with CRR induced initial reaction, which was resolved with 300 mg PO aspirin. Two patients with initial type I reactions developed chills and fever 12 h after finishing the protocol, and the other developed back pain in two separate occurrences 18 and 24 h after completed the protocol, they were treated with paracetamol and ibuprofen respectively (Table S2).

3.5 | Biomarkers: tryptase and IL-6

Tryptase levels were increased during the initial reactions in 15 patients (Table 2A). The mean initial reaction tryptase for carboplatin

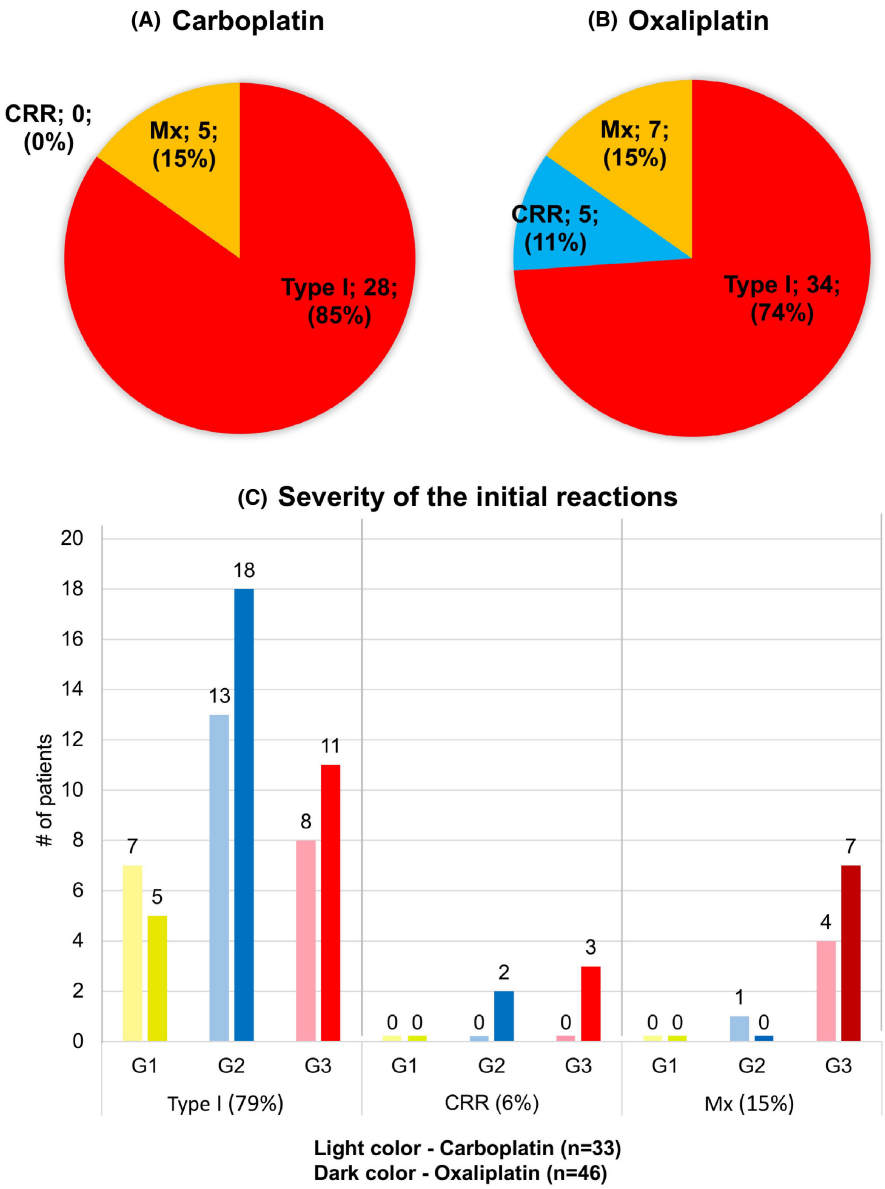


FIGURE 1 Phenotype presentation and severity during initial reactions. CRR, cytokine release reactions; G1, grade 1; G2, grade 2; G3, grade 3. (A) Initial phenotype in carboplatin-allergic patients; (B) Initial phenotype in oxaliplatin-allergic patients; (C) Severity of initial reactions according to phenotypes.

type I phenotype was 11.8 μg/L ± 7.7 and 6.8 μg/L ± 2.6 for oxaliplatin. These values were statistically significant when compared to the patient's baseline tryptase values (Table 2A).

The mean BTR tryptases collected were 8.2 μg/L ± 3 for carboplatin, $p = .02$; 10.7 μg/L ± 6.7 for oxaliplatin, $p = .04$. Oxaliplatin-treated patients with Mx had significant elevation of BTRs tryptase of 10.2 μg/L ± 2.7 (Table 2A).

In oxaliplatin-treated patients presenting with initial CRR for whom IL-6 was available had a mean baseline IL-6 level of 10 pg/mL (Table 2B), and significant changes in IL-6 were observed in BTRs ($p < .01$) (Table 2B).

3.6 | Phenotype switching and protocol transition/adaptation

85% of first carboplatin protocols and 56% of initial oxaliplatin protocols were tolerated without BTRs ($p < .01$).

DD for carboplatin reactive patients was done with 4bags/16 steps and 3 bags/12 steps protocols based on risk stratification. Twelve carboplatin-allergic patients were classified as a G3 initial reaction, of these, 5 who had presented hypertension without other changes in vital signs were initially treated with a 3-bag/12 steps protocol while the other 7 were treated with 4-bag/16 step protocol. In addition, all patients with G1 (7) and G2 (14) reactions were initially treated with a 3 bag/12 step protocol and 71% were completed without reactions (Figure S2).

Twenty-one oxaliplatin-allergic patients presented G3 reactions, 12 of these patients were treated with 3-bag/12 steps protocol while the other 9 were treated with 4-bag/16 step protocol. In addition, on 20 patients with initial G2 and 3 patients with initial G1 reactions, DD was done with 3 bags/12 step protocols, and on 2 patients with G2 initial reactions a 2 bags/8 step protocol was done (Figure S2).

Modifications to the carboplatin protocols were made in 20/26 protocols (77%) with increases in the infusion rate (up to 160 mL/h)

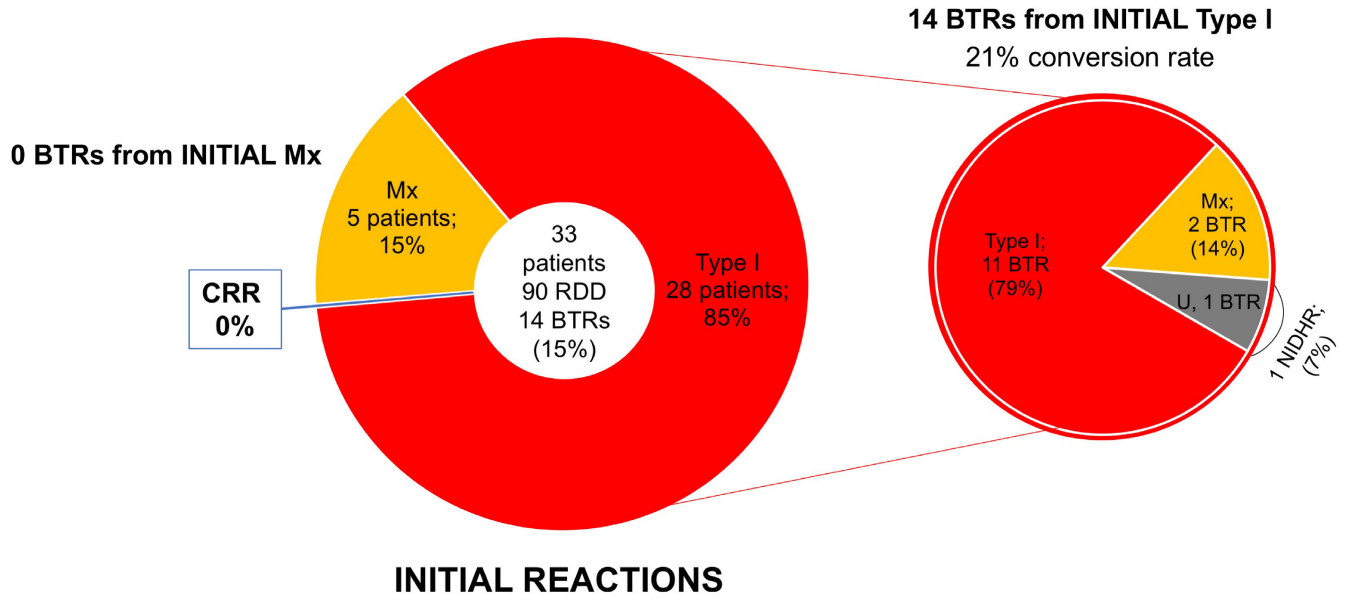


FIGURE 2 Phenotype conversion during carboplatin desensitization breakthrough reactions.

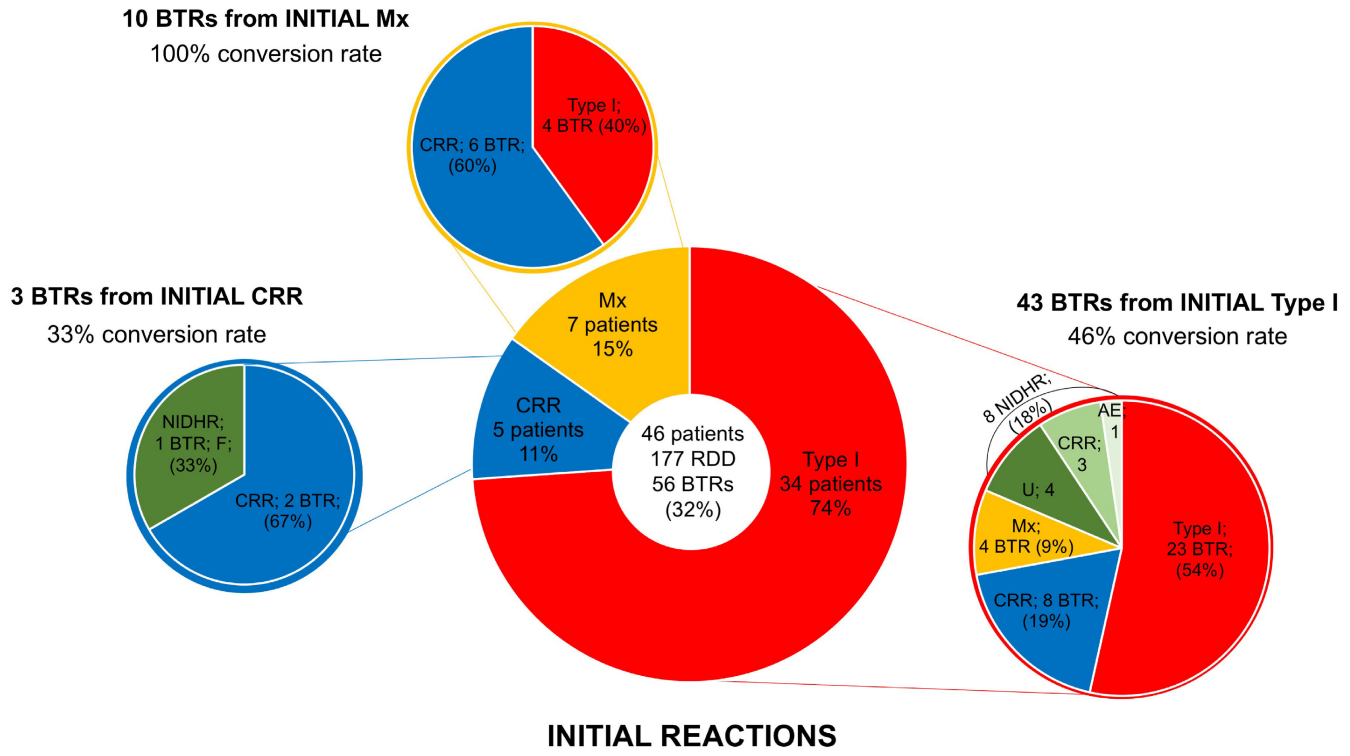


FIGURE 3 Phenotype conversion during oxaliplatin desensitization breakthrough reactions. BTR, breakthrough reactions; CRR, cytokine release reactions; F, non-immediate flushing; Mx, mixed phenotype; NIDHR, non-immediate drug hypersensitivity reactions; RDD, rapid drug desensitization; U, non-immediate urticaria; AE, non-immediate angioedema.The central graph shows in the white circle general information for each platin, including the number of patients, number of desensitizations and total BTRs. The same graph shows the initial characteristics of the different phenotypes: In red, type I; in yellow, Mx; and in blue CRR. The peripheral graphs show the phenotypes developed during BTRs; in these, the non-immediate reactions and their characteristics are shown in green.

and a decrease in the number of bags when no BTRs occurred, while in 28/31 protocols no changes were made. For oxaliplatin protocols, 58/67 (87%) had increases in the infusion rate (up to 160 mL/h) and decrease in the number of bags due to no BTR, while 37/64 (58%) protocols were not changed (Figure S2).

4 | DISCUSSION

This is the first direct comparison between carboplatin and oxaliplatin initial DHRs and their response to DD. We uncover carboplatin phenotypes including Mx reaction during initial presentation and

TABLE 2 (A) Changes in serum tryptase levels in carboplatin and oxaliplatin during initial and desensitization BTR. (B) Changes in serum IL-6 levels in carboplatin and oxaliplatin initial and BTR.

(A)

	Carboplatin			Oxaliplatin		
	Baseline ($n=26$)	IR ($n=12$)	BTR ($n=7$)	Baseline ($n=34$)	IR ($n=21$)	BTR ($n=23$)
Phenotype	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Type I	4.3 ± 2.6	11.8 ± 7.7*	8.2 ± 3*	4.3 ± 1.6	6.8 ± 2.6*	10.7 ± 6.7*
Mx	7.8 ± 4	–	4.8 ± 0.9	4.7 ± 1.5	10.2 ± 2.7*	3.8 ± 1.2
CRR	–	–	–	4.4 ± 0.8	6.5	2.04 ± 0.7

(B)

	Oxaliplatin		Carboplatin	
	Baseline ($n=7$)	BTR ($n=10$)	Baseline ($n=13$)	BTR ($n=2$)
Phenotype	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
CRR	10	6659.5 ± 9026.2*	–	–
Mx	–	39.4 ± 55.3*	8 ± 5.7	–
Type I	3.7 ± 0.5	8.9 ± 4.1	6.4 ± 4.6	3.9 ± 2.8

Note: (A) IL-6 levels are expressed in pg/mL. IL-6 normal value <10 pg/mL. *Significant IL-6 elevation. (B) Tryptase levels in μg/L. Tryptase normal value <11.4 μg/L. *Significant tryptase elevation (above the normal limit and baseline tryptase X1.2 + 2).

Abbreviations: BTR, breakthrough reactions; CRR, cytokine release reactions; IR, initial reactions; Mx, Mixed phenotype; SD, standard deviation; Type I, phenotype 1.

provide the range of oxaliplatin phenotypes (type I, CRR, and Mx). We observed phenotype switching from type I to Mx for carboplatin and to Mx, CRR, and NIDHR for oxaliplatin. CRRs were exclusively observed in oxaliplatin-reactive patients, and Mx were almost double when compared to carboplatin.

Our findings support previous studies indicating that DD to carboplatin and oxaliplatin is safe and effective.[3,4,6,8,11,14] Skin testing was positive in 75% of carboplatin-allergic patients and the phenotypes were consistent with type I reactions which supports an IgE-mediated mechanism.[6,15,23] Patients allergic to carboplatin are more atopic, reported to have higher levels of serum IgE, and require repeated exposures to the drug before reacting.[24,25] The phenotypes and biomarkers of carboplatin reactions suggest a TH2 immune deviation and an IgE/mast cell endotype of most initial and BTR reactions. Reactions to oxaliplatin are more heterogenous with type I, CRR, Mx, and NIDHRs. Previous studies reported symptoms of fever, chills, and rigors in 19% of oxaliplatin reactions similar to our patients with a CRR phenotype.[4,26]

Oxaliplatin phenotype switching during DD has been described before, supporting the notion that DD blocks IgE-dependent mast cell activation mechanisms, and that oxaliplatin can trigger other immune cells and mechanisms during DD.[4] In the oxaliplatin-allergic group, more advanced stages of cancer were observed. Previous reports have linked increased serum IL-6 concentrations with advanced colorectal cancer and decreased survival. Increases in this biomarker may play a role in both allergic reactions to oxaliplatin and tumor responses.[27,28]

Type I reactions to carboplatin and oxaliplatin were associated with elevated tryptase levels, and CRR reactions and Mx to oxaliplatin were associated with elevated IL-6 levels. Increased serum levels of IL-6 were associated with oxaliplatin CRRs and Mx and correlated with the severity of reactions (Table 2B). While the cellular origin has not been uncovered, mast cells, macrophages, monocytes, dendritic cells, and Langerhans cells have IgE and IgG receptors which can activate with preferential release of cytokines such as IL-6, which correlated with non-classical symptoms such as fever, chills, pain, and hypertension.[29]

Overall, carboplatin-allergic patients tolerated initial DD protocols well with no need for modifications as opposed to oxaliplatin-allergic patients who required protocol modifications to prevent BTR reactions. Oxaliplatin patients who had CRR reactions were switched to a 2-bag/8-step protocol with improved outcomes suggesting that CRRs could benefit from protocols with fewer bags.

Based on this study and previous observations,[4,26] we propose an algorithm with reduction in the number of bags, potentially including a 1 bag/4 step for patients with CRR who did not experience BTRs during the 3/12 steps and 2 bag/8 step protocols.

Symptom targeted premedication is recommended, including the use of steroids, NSAIDs, and fluids for CRRs. Protocols with 3 bag/12 step or 4 bag/16 step protocol are recommended for type I or Mx reactions based on risk, and a lower number of bags is recommended for CRR. Future studies are needed to evaluate the safety of starting DD for CRR reactions with reduced number of bags. For patients with high risk DD refractory to premedication and bags adjustments, omalizumab may be helpful for type I,[30–33] while the use of tocilizumab, which blocks IL-6, may be helpful for CRRs[34] (Figure 4).

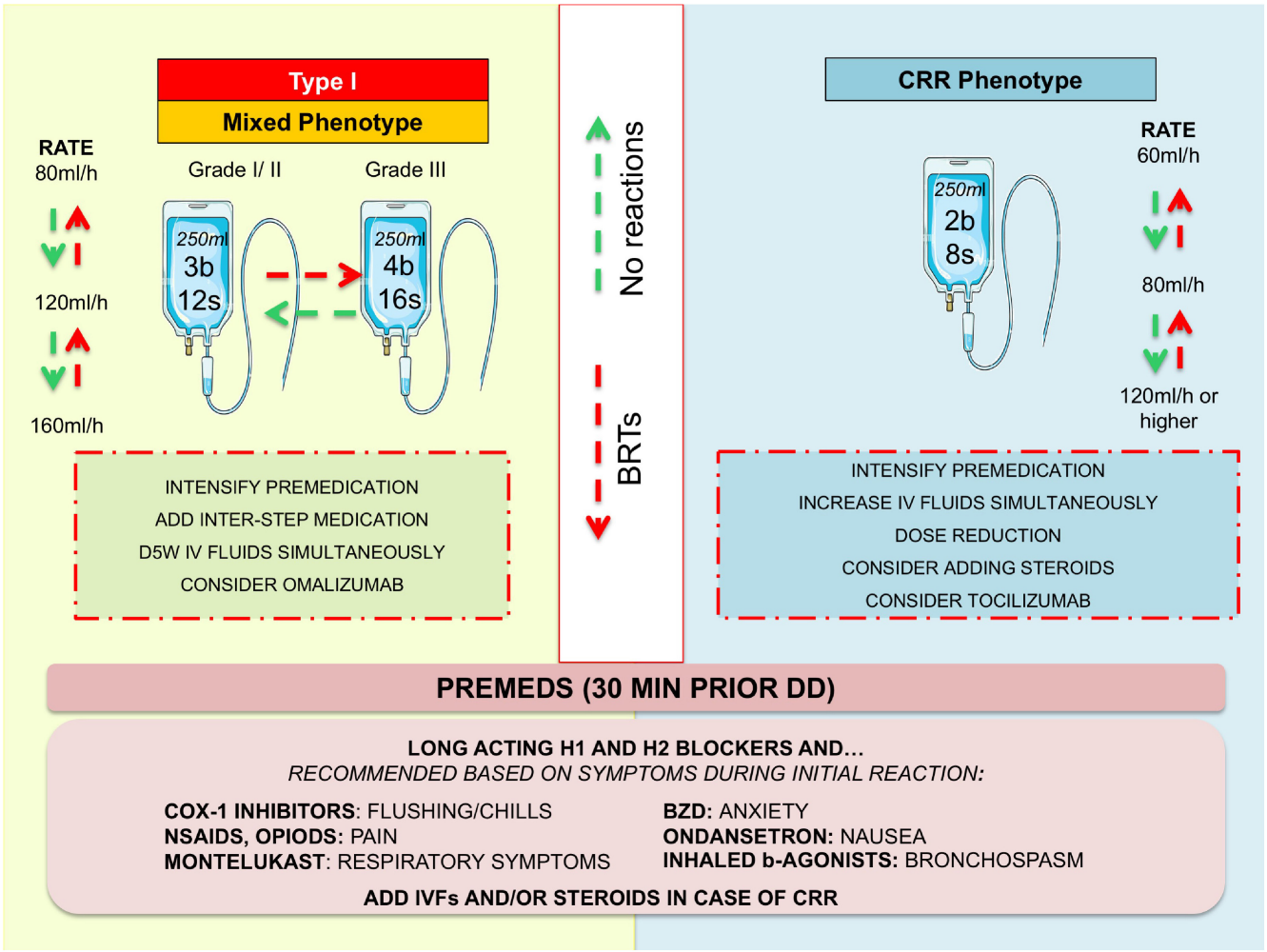


FIGURE 4 Proposed algorithm for escalation and de-escalation of carboplatin and oxaliplatin desensitization protocols. b, bags; BTR, breakthrough reactions; BZD, benzodiazepines; CRR, cytokine release reactions; DD, drug desensitization; s, steps. Premeds should be administered 30 min prior to desensitization based on symptoms presented in the initial reaction. The choice of the ideal protocol will depend on the initial endophenotype with changes in future desensitizations depending on tolerance. The final infusion rate will depend on patient tolerance and pharmacy recommendations for the administration of each drug.

An important limitation of this study was the low number of patients with CRR and Mx, and the limited availability of biomarkers.

This study emphasizes a distinctive pattern of phenotypes in DHR to carboplatin and oxaliplatin and provides evidence of phenotype switching during DD-BTRs. Accurate endophenotyping is critical to address specific DDs protocols. Carboplatin DHRs are consistently type I, whereas oxaliplatin DHRs have variable phenotypes that can undergo switching during DD. This study confirms the notion that oxaliplatin has atypical presentations with "transformer" capacity during DD.[4,35]

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Teodorikez-Wilfox Jimenez-Rodriguez; Leticia de las Vecillas; Marina Labella; Donna-Marie Lynch, Kylie Marie Besz and Mariana Castells; data collection: Amparo Burgos, Victor Soriano Gomis, Inmaculada Lozano, Rosa Ana Montoyo Antón, Francisco Marco de la Calle, María Purificación González Delgado, Aurora Gutiérrez, Estefanía Montenegro, Fernando Rodríguez, Francisco Javier Fernández Sánchez; analysis and interpretation of results: Teodorikez-Wilfox Jimenez-Rodriguez; Leticia de las Vecillas; Marina Labella; Donna-Marie Lynch, Kylie Marie Besz; Kathleen Marquis and Mariana Castells; draft manuscript preparation: Teodorikez-Wilfox Jimenez-Rodriguez; Leticia de las Vecillas; Marina Labella; Donna-Marie Lynch, Kylie Marie Besz, Kathleen Marquis and Mariana Castells. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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